

# USP Standards for Complex Generics

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## The global landscape of complex generics

A web survey of global Medicines Regulatory Authorities (MRAs) found that beyond the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), there is no explicit recognition of a distinct category of products (complex generics or hybrid medicines) requiring particular studies to demonstrate their equivalence with innovator products, as shown in **Table 1**.

Table 1. MRAs regulatory approaches for the approval of complex generics

<b>U.S. FDA</b>	<ul style="list-style-type: none"> <li>Establish categories of complex products for the purpose of development of generics (Manual of Policies and Procedures (MAPP) 5240.10)</li> <li>Support through Generic Drug User Fee Amendments (GDUFA), currently GDUFA III (2022-2027)</li> <li>Research collaborations to address specific needs [e.g., Center for Research on Complex Generics (CRCG)]</li> <li>Product Specific Guidances (PSGs) detailing required additional studies</li> </ul>
<b>EMA</b>	<ul style="list-style-type: none"> <li>Defines hybrid medicines as different entities than 'generics'</li> <li>Partial overlap with FDA's classification for complex generics</li> <li>Several approval pathways in European Union (centralized, decentralized, mutual recognition, or national procedures)</li> <li>Guidance for specific products</li> </ul>
<b>Canada</b> <b>Australia</b>	<ul style="list-style-type: none"> <li>Non-regulatory documentation refers to the category of complex products or U.S. FDA and EMA processes</li> <li>No overarching regulatory recognition of products/categories presenting different challenges than 'classic' generics (e.g., solid oral dosage forms of small molecules or aqueous injections)</li> </ul>
<b>Africa</b> South Africa <b>America</b> Argentina; Brazil; Colombia; Mexico; Peru <b>Asia</b> China; India; Japan; Korea; Singapore <b>Europe</b> UK; Russia; Spain; Switzerland	<ul style="list-style-type: none"> <li>No overarching regulatory recognition of products/categories presenting different challenges than 'classic' generics (e.g., solid oral dosage forms of small molecules or aqueous injections)</li> </ul>

Despite the lack of explicit recognition of the challenges for development and approval of products included under U.S. FDA complex products categories, complex products in all categories are available in many of these countries. Furthermore, several countries have quality information and bioavailability guidelines addressing the needs for certain type of products within some of these categories.

What is available?

- ▶ Focused initiatives at certain regulatory agencies (EMA; Health Canada; Therapeutic Goods Administration (TGA); U.S. FDA)
- ▶ Discussion groups and workshops with multiple relevant stakeholders (e.g., Non-Biological Complex Drugs Working Group; NY Academy of Science; CRCG)
- ▶ Pilot Program: EMA-U.S. FDA Parallel Scientific Advice for Complex Generics/Hybrid Medicines

International regulatory fora are not addressing global regulations, convergence or harmonization for the multiple categories defined by U.S. FDA

- ▶ No mention at the International Coalition of Medicines Regulatory Authorities (ICMRA)
- ▶ At the International Pharmaceutical Regulators Programme (IPRP) the Nanoparticles Working Group addresses countries regulations *specific only* for the complexity posed by nanoparticles
- ▶ ICH included the need to address certain complex products in a 2018 Reflection Paper and in a subsequent timeline for future development (2021), but no harmonization process has been initiated yet

## Complex generics in USP-NF: Current status

The USP-NF contains compendial documents supporting complex generics development, with over 250 official monographs for complex generic drug products and general chapters. These resources serve as a robust starting point to expand with more focused complex generic standards tailored to industry needs.

## What is in USP pipeline for complex generics?

USP identifies current priorities for compendial guidance based on extensive consultation with multiple stakeholders to address industry and regulatory needs. Top USP priority categories for complex generics are complex injectables, including liposomes and microspheres, and extractables & leachables (E&L).

Complex injectables provide benefits across therapeutic areas and can improve patient compliance, but many of these injectables currently lack generic competition. The FDA has made developing complex injectables like long-acting injectables (LAIs) a priority by supporting research on associated challenges through GDUFA research.

The other priority area of E&L requires new USP reference standards, testing guidance documents, and system suitability standards to support industry needs. Around 60% of E&L testing is outsourced, highlighting the need for compendial guidance. In the Pharmacopeial Forum, PF 49(4), a stimuli article entitled "Proposals for the Development, Composition, and Routine Use of System Suitability Standard Mixtures in Support of Chromatographic Screening for Organic Extractables and Leachables" was published, and the full article is available on PF Online via the [USP Website Access Point](#).

USP supports ongoing dialogue and collaboration between MRAs and pharmacopeias to identify priority areas for alignment, convergence, and harmonization efforts related to complex generics for globally consistent and efficient regulatory processes.

### Upcoming Events

- Development of Standards for Complex Excipients (Presentation), USP's iterative approach on modern analytical methods for polymeric excipients (Rapid Fire), Compendial Strategy to Define Composition and Quality of Polysorbates (Poster) at [PharmSci 360 - American Association of Pharmaceutical Scientists \(aaps.org\)](#) in person at the Orange County Convention Center in Orlando, FL on October 22 to 25, 2023.
- [Characterization of Complex Excipients/Formulations Workshop](#) in person and virtual at The Universities at Shady Grove in Rockville, MD on December 7 - 8, 2023

For ongoing updates and to learn more, click here: <https://www.usp.org/complex-generics>

### Resources

1. United States Pharmacopeia. 2023. Addressing barriers to the development of complex generics: Understanding Challenges and Opportunities. Available at: [https://www.usp.org/sites/default/files/usp/document/ea83b\\_complex-generics\\_wp\\_2023-07\\_v3.pdf](https://www.usp.org/sites/default/files/usp/document/ea83b_complex-generics_wp_2023-07_v3.pdf)
2. Gruddanti, P. Complex generics: The need and the challenges. (2023, June 12). Available at: <https://qualitymatters.usp.org/complex-generics-need-and-challenges>.
3. Pribluda, V. Complex generics: Are global regulators addressing the needs? (2023, June 26). Available at: <https://qualitymatters.usp.org/complex-generics-are-global-regulators-addressing-needs>.
4. Pribluda, V. Radwick, A. and Koduri, C. Global regulatory landscape of complex generics. Poster presented at: Drug Information Association (DIA) Annual Meeting, June 27, 2023; Boston, MA. Available at: <https://www.usp.org/sites/default/files/usp/document/public-policy/fda-categories-of-non-biological-complex-products.pdf>.
5. Pribluda, V. Radwick, A. and Koduri, C. Global regulatory landscape of complex generics study summary. (2023, June 27). Available at: <https://www.usp.org/sites/default/files/usp/document/handout-global-landscape-of-complex-generics.pdf>.
6. United States Pharmacopeia. Stimuli article: Proposals for the Development, Composition, and Routine Use of System Suitability Standard Mixtures in Support of Chromatographic Screening for Organic Extractables and Leachables. Pharmacopeial Forum, PF 49(4). Available at: [https://go.usp.org/l/323321/2023-07-07/91k9sb/323321/1688732045g0a9O4Pr/System\\_Suitability\\_Standard\\_Mixtures\\_in\\_Support\\_of\\_Chromatographic\\_Scr.pdf](https://go.usp.org/l/323321/2023-07-07/91k9sb/323321/1688732045g0a9O4Pr/System_Suitability_Standard_Mixtures_in_Support_of_Chromatographic_Scr.pdf).

### About USP

USP is an independent, scientific, global non-profit organization founded in 1820 when eleven physicians took action to protect patients from poor-quality medicines. Convening in the old U.S. Senate Chamber, they published a national, uniform set of guidelines for medicines called the U.S. Pharmacopeia. A core pillar of USP's work is to help strengthen the global supply chain so that the medicines, dietary supplements, and foods that people rely on for their health are available when needed and meet quality standards as expected and required.

The Federal Food, Drug, and Cosmetic Act of 1938 created the statutory requirement that medicines sold in the United States generally must adhere to USP's public quality standards to help ensure the quality of medicines and the safety of patients. USP standards are developed by nearly 800 scientific and healthcare experts who volunteer their time on USP's standard-setting committees, which also include over 200 U.S. Food and Drug Administration (FDA) government liaisons. In these and other ways, USP works closely with the FDA, other government agencies, and across health and science communities to develop USP standards (over 6,000 today) that are enforced by the FDA.

In addition to our work on standards, USP is an active participant in many public-private partnerships on supply chain-related issues. This includes work with the FDA, Administration for Strategic Preparedness and Response (ASPR), and the Biomedical Advanced Research and Development Authority (BARDA). USP also engages with the World Health Organization and the Pan American Health Organization as an officially recognized non-state actor and hosts the USP-APEC (Asia-Pacific Economic Cooperation) Center of Excellence for Securing Medical Product Quality through the Supply Chain, under the sponsorship of the FDA.

USP is governed by more than 500 organizations, including scientific, healthcare practitioner, consumer, and industry organizations, as well as dozens of government agencies, who together comprise the USP Convention.